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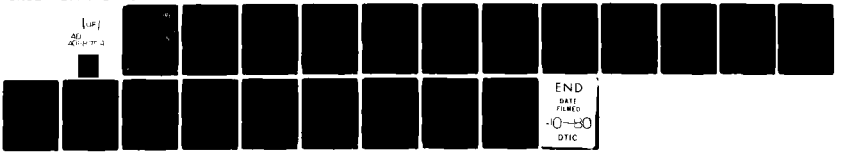

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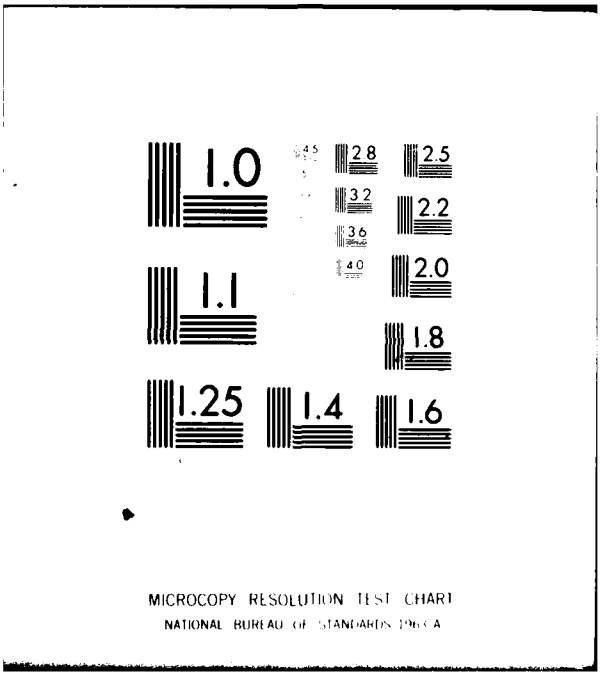
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REPORT NUMBER 6

LEVEL II

SYNTHESIS OF 6-SUBSTITUTED-2, 4-DIAMINO-5,6,7, 8-TETRAHYDROPYRIMIDO (4,5-d) PYRIMIDINES

Annual Report

THOMAS J. DELIA

October 1979

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Central Michigan University
Mt. Pleasant, Michigan 48849

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REPORT DOCUMENTATION PAGE

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Arylamines
Benzylamines
Benzylhydroxylamines
Phenylethylamines
Antimalarial
Antitrypanosomal

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

A series of sixteen target compounds involving primarily methylene, ethylene and methyleneoxy spacers between the heterocyclic portion and halogenated phenyl portion were prepared and submitted for screening. The chemistry and biological screening results are described. None of the compounds exhibited useful chemotherapeutic activity.

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FORWARD

During the period since the last Annual Report (September 1978) the major portion of the target compounds which lent themselves to synthesis according to the proposed route were prepared and evaluated for antimalarial activity. Modifications were occasionally made in either general approach or target compound with the consent of the program monitor.

The work in progress at present represents an agreed upon departure from the remaining target compounds proposed. This is based on the negative screening results obtained so far. Thus, an attempt will be made to portray the completed work as a summary report since further work on these compounds is not anticipated. There may be some overlapping between this report and the previous annual report which is unavoidable and, perhaps, even desirable.

TECHNICAL REPORT

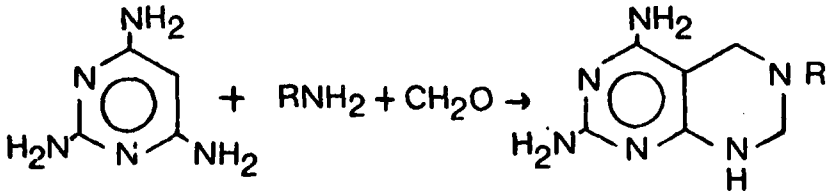
I. Statement and Background of the Problem

In the previous Annual Report (August 1978) the biological rationale was detailed. In essence the formulation of 5, 6, 7, 8-tetrahydropyrimido [4, 5-d] pyrimidines as potential antimalarial agents is based on analogy to other series which possess antifolate activity (1).

The two dimensional chemical structure bears a strong resemblance to the aromatic quinazolines which are the foremost compounds studied in this area. However upon examination of molecular models a quite different picture emerges. While it is possible to place the two fused fings in a nearly planar arrangement the 6-substituent must lie out of the plane. Thus, we have an opportunity to examine the coplanar requirements of the six substituent.

II. Approach to the Problem

The proposed chemical synthesis of the title compounds has been previously described. By way of review the sequence involves the following:



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The adjacent 6-NH_2 group is a necessary component of this reaction. We have investigated other pyrimidines in which the 2- and 5- substituent were varied and did not always include the NH_2 group and found the reaction to proceed to the corresponding 5, 6, 7, 8-tetrahydro [4,5-d] pyrimidines.

Before we began this work we did not expect any difficulties with the various amines proposed. However, it is now clear that each series of amines has a different feature which provides for poor to excellent results.

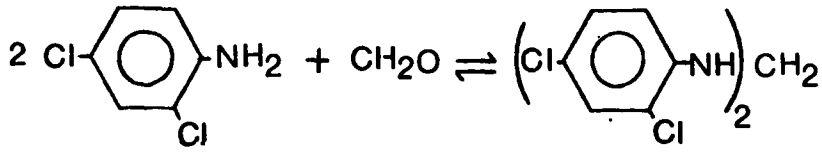
III. Discussion of Results

A. Reaction of 2, 4, 6-Triaminopyrimidine with Substituted Amines

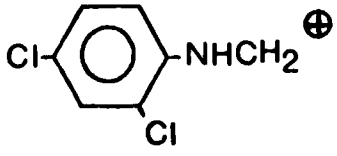
1. Anilines

Based on previous experiences (2) with the reaction of p-anisidine in this reaction it was felt that the reaction with other substituted anilines would be feasible. While the desired pyrimido [4, 5-d] pyrimidine was obtained with p-anisidine (2), a variety of halogenated aniline derivatives failed to give the corresponding pyrimidine compounds. The anilines used in our studies were the 2-chloro, 3-chloro 4-chloro, 2,4-dichloro and 3,4-dichloro derivatives with particular emphasis on the 4-chloro and 2,4-dichloro analogs. Variations in the conditions employed included solvent medium, temperature, form of the formaldehyde, pH changes with acid or base catalysis.

The corresponding methylene bis anilines were prepared, according to the method of Bischoff and Reinfeld (3), since these were felt



to be the requisite intermediates in the Mannich process. Under neutral or basic conditions these could be prepared in approximately 80%. The yields were considerably lower under acidic conditions. However acid conditions were necessary for decomposition of the methylene bis anilines to the reactive intermediate,



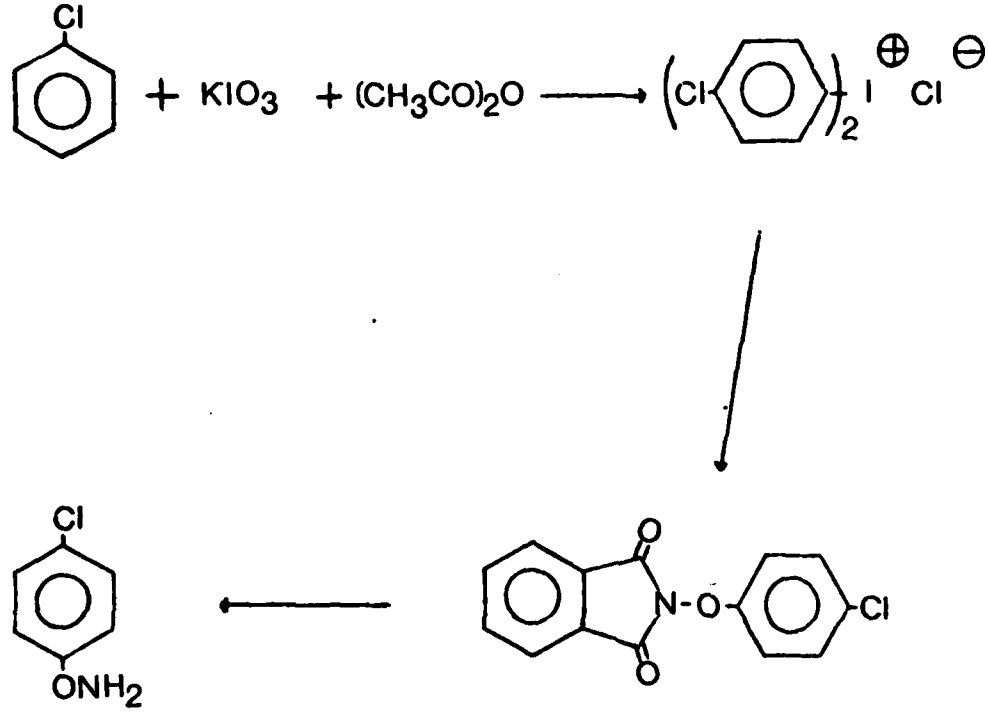
In reality, the acid merely served to push the equilibrium back toward starting materials. Clearly the deactivation of the substituent

halogen atoms is significant and prevents the formation of the desired intermediate. Alternate methods for preparation of 6-x-phenyl-2, 4-diamino-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidines are being investigated.

2. O-Arylhydroxylamines

A survey of literature indicated that there were no general methods for the synthesis of these compounds (4). Isolated examples were reported for a few compounds which either were in error or proceeded in poor yield.

One example was prepared in the following manner (5):

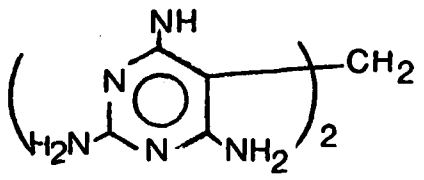


The overall yield of this reaction was 36%.

Upon treatment of 2,4,6-triaminopyrimidine with this aryloxyamine under a variety of conditions 4-chlorophenol was the major isolable product. Treatment of the 5-chlorophenoxyamine in refluxing ethanol with acid or base catalysis resulted in cleavage to produce 4-chlorophenol. The instability of this compound under conditions necessary for Mannich reaction discouraged any attempt to synthesize other O-arylhydroxylamines. Alternate methods for the preparation of 6-x-aryloxy-2, 4-diamino-5,6,7, 8-Tetrahydropyrimido [4,5-d] pyrimidines are desirable.

3. Benzylamines

Treatment of one equivalent of 2,4,6-triaminopyrimidine with two equivalents of formaldehyde and two equivalents of the corresponding benzylamine provided the desired 6-x-benzyl-2, 4-diamino-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidines in excellent yields. The compounds obtained in this manner and their physical data are shown in TABLE 1. The use of only one equivalent of either amine or formaldehyde led to a poor yield of the desired products and an unwanted side product,



Further, if the amine and formaldehyde are not premixed before addition of 2,4,6-triaminopyrimidine this bis triaminopyrimidyl methane is also formed in significant quantities.

4. O-Benzylhydroxylamines

The reaction of 2,4,6-triaminopyrimidine with O-benzylhydroxylamines and/either formalin or polyoxymethylene under acid-catalyzed conditions provides moderate yields of the corresponding 6-benzyloxy-2, 4-diamino-5,6,7, 8-tetrahydropyrimido [4,5-d] pyrimidines. These products are also indicated in Table 1. It was not possible in this series to completely eliminate the formation of the bis pyrimidylmethane side product (6). This product and cleavage of the O-C bond leading to 6-hydroxy-2, 4-diamino-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidine accounted for the poorer yield of these benzyloxy compounds.

The requisite O-benzylhydroxylamines were usually prepared from the corresponding benzyl halides and N-hydroxyphthalimide, followed by hydrazinolysis of the phthalimide intermediate.

5. Phenylethylamines

The reaction of 2,4,6-triaminopyrimidine with phenylethylamines and formalin in a ratio of 1:2:2 behaved as in the benzylamine series. The reaction proceeds best in a basic medium and yields of 6-x-phenylethyl-2, 4-diamino-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidines were excellent. These products were summarized in Table 1.

The phenylethylamines were usually prepared by hydride reduction of the corresponding benzyl cyanides.

6. Miscellaneous Amines

a. Miscellaneous Aralkoxy and Aryloxyalkyl amines.

The reaction of 2,4,6-triaminopyrimidine with 2-(chlorophenyl)-ethoxyamine and formaldehyde was successfully employed to form 6- [2-(4-chlorophenyl)ethoxy] -2,4-diamino-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidine in 62% yield. A similar reaction using 2-(2,4-dichloro phenyloxy ethoxyamine was successful, although the yield was only 22%. In both cases significant quantities of the previously mentioned bis pyrimidyl methane were isolated.

Other attempts utilizing either one or two oxygens in the space between the amine function and the aryl moiety have been made. On the whole considerable difficulty was encountered with either the synthesis of the requisite amine or the subsequent reaction with 2,4, 6-triaminopyrimidine. These will not be detailed further since they were not pursued to a final conclusion.

b. Hydroxylamine

The reaction between 2,4,6-triaminopyrimidine and hydroxylamine with formaldehyde was investigated. The product from this reaction, 6-hydroxy-2, 4-diamino-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidine, could be used as an intermediate in those series which proved difficult. These involved the N-O-C system which we found to be susceptible to cleavage at the O-C bond.

The compound was ultimately isolated in 70% yield by allowing the mixture to remain at room temperature for one week. Satisfactory elemental analysis of this compound has not yet been achieved because of solvent contamination and decomposition in air by the molecule.

c. 2-Hydroxybenzylamine

The synthesis of 6-(2-hydroxybenzyl)2,4-diamino-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidine was attempted. This new target compound arose from discussions with Dr. Richard E. Strube in which

the particular arrangement of the N-CH_2-C=C-OH function was deemed a possible active variation of our hitherto unrewarding benzyl series. The 2-methoxy and 2-benzyloxy derivatives were utilized, in turn, to try to achieve this synthesis. Each of these compounds participated in the formation of the corresponding 6-substituted pyrimido [4,5-d] pyrimidine. However either decomposition or very poor yields were associated with all attempts to remove the blocking groups. This approach was finally abandoned.

Biological Data

To date sixteen target compounds have been submitted for screening. These compounds and their corresponding code numbers and bottle numbers are shown in TABLE 2.

1. Antimalarial Screening.

Fifteen of the sixteen compounds submitted (except P) have been screened in the standard rodent procedure (7). None of the target compounds exhibited sufficient activity to warrant continuation of the series. In the case of compound N a certain degree of low level activity was noted. However this could not be substantiated upon re-screening. In all, twelve compounds exhibited some degree of toxicity at the higher doses examined, i.e., 160 or 640 mg/kg.

2. Antitrypanosomal Screening.

Of the sixteen compounds submitted sufficient material was available to permit screening in this system for eight derivatives (B, F, G, I, J, K, L, M, O). None of these compounds exhibited activity in the Rane/Ager test system (8).

Conclusions

In view of the negative results obtained so far with a series of 2,4-diamino-6-substituted-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidines we are drawn to a number of conclusions.

Since one of the rationales for proposing this series of compounds was the potential antifolate activity it is surprising to find little antimalarial activity which would presume this enzyme inhibition. On the surface there appears to be very little difference in the ring system proposed, namely the tetrahydropyrimido [4,5] pyrimidine and the tetrahydropteridine ring of folic acid. An examination of molecular models does indicate that the N-substituent would necessarily have to lie out of coplanarity with the ring system albeit still equatorial. This is true for both ring systems.

There is another factor involving spatial relationships. The compounds tested so far possess from one to four atoms intervening between the chlorinated phenyl ring thought to be necessary and the reduced heterocyclic ring system. There does not appear to be any informative pattern in the biological response. A majority of members of each class exhibit some toxicity at high dose levels without any indication of useful activity at lower levels. Thus we have to con-

clude that an essential feature of antimalarial activity is missing.

Based on the foregoing biological results and conclusions we do not see continuation of further members of the original target compounds as cost effective. Because of extreme difficulties and time-consuming efforts in the preparation of various x-phenylpropylamines and x-phenylpropyloxyamines we have abandoned these remaining target compounds.

Recommendations.

Many of the active compounds to which this series may be compared possess at least one nitrogen atom in the side chain. These active species include, among others, primoquine (9), quinacrine (10) and amodiaquine (11).

Therefore we recommend that the initial concept and rationale for the approach taken thus far be continued. However, a new set of target compounds bearing at least one nitrogen atom in the space between the chlorinated phenyl ring and the reduced heterocyclic moiety is proposed. These new compounds could include examples such as -NHAr , $-CH_2NHAr$, $-CH_2CH_2NR_2$, and $-CH_2CH_2NHCH_2CH_2NR_2$.

Some preliminary experiments devoted to this approach have already been made.

Experimental

Melting points are uncorrected. PMR Spectra were recorded in $DMSO\text{-}d^6$ on a Varian T-60 spectrometer with TMS as internal standard. Mass spectra were performed by The Walter Reed Army Institute of Research. All the benzylamines used were available commercially. The phenylethylamines used are known and were prepared by the $NaBH_4$-$CoCL_2$ reduction of the corresponding cyano compound (12). The benzylhydroxylamines are also known and were prepared according to a known general procedure (13).

General Method for the preparation of 2,4-diamino-6-aralkyl-5,6,7,8-tetrahydropyrimido [4,5-d] pyrimidines (compounds A-J):

A mixture of two equivalents of the appropriate amine and two equivalents of formalin (37%) was shaken at room temperature without solvent for 15 minutes. The gummy material obtained was then treated with a solution of one equivalent of 2,4,6-tiaminopyrimidine in ethanol. After refluxing for 24 hrs. the clear reaction mixture was evaporated under reduced pressure and the gummy residue solidified upon washing once with petroleum ether ($63\text{-}74^{o}$) followed by ether several times. In some cases, after washing with petroleum ether, the gummy material was dissolved in the least amount of MeOH (cases E and G) or ether (case J) and the resulting solution was allowed to stand in the refrigerator for 24 hrs. to give a white crystalline material. Purification of the products was achieved by several crystallizations from the proper solvent or by silica gel column chromatography solvents used were $CHCL_3$-MeOH (9:1), (8:2) or (7:3) followed by crystallization. When a mixture of 3,4, dichlorobenzylamine (0.88 g, 5 mmole) and 37% formalin (0.41g 5 mmole) was treated with a solution of 2,4,6-triaminopyrimidine (0.625 g, 5 mmole) in 30 ml Etanol and the resulting solution was heated under reflux for about 2 hrs. a white precipitate formed. After continued refluxing for 24 hrs the reaction mixture was cooled to room temperature and the white precipitate (0.35g) was filtered and recrystallized from dimethylsulfoxide or water (sparingly soluble). This material is 5,5 methylene bis 2,4,6-triaminopyrimidine, m.p. 360. The PMR spectrum indicated absorptions at $\delta 3.34$ ($2H, S, -CH_2$), $\delta 5.3$ ($2H$, S, NH_2 at position 2), $\delta 5.6$ ($4H$, S, NH_2 at positions 4 and 6). The mass spectrum show major ions at me 262 (M^+), m e 138, 125 and 110. The ethanol filtrate upon evaporation and the residue treated as described gave 0.5 g of A.

General Method for the preparation of 2,4-diamino-6-aralkoxy-5,6,7, 8-tetrahydropyrimido [4,5-d] pyrimidines (compounds K-P).

A mixture of two equivalents of the appropriate hydroxylamine hydrochloride derivative and two equivalents of polyoxymethylene was refluxed in 95% ethanol (14) while stirring for 5 hr. The oxime solution thus obtained was treated with a solution of one equivalent of 2,4,6-triaminopyrimidine in ethanol. After refluxing and stirring for 2 hrs. a white precipitate separated from the reaction medium. Refluxing and stirring was continued for 36 hrs. The cold (room temperature) reaction mixture was made alkaline by stirring with sodium hydroxide pellets at room temperature and the insoluble precipitate was filtered. This included the methylene bis-2,4,6-triaminopyrimidine. The ethanol filtrate was evaporated under reduced pressure and the residue obtained was washed with ether then purified either by several crystalli zations (case L) or by chromatography on a silica gel column (solvent $CHCL_3$-

MeOH, 9:1) followed by crystallization from an appropriate solvent to give the title compounds.

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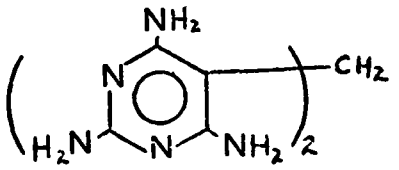
6. We have mass spectral evidence but not satisfactory elemental analysis for a compound of the following structure,



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14. Absolute ethanol used in the preparation of compound O.

TABLE I
Summary of Compounds Submitted for Screening

II	R	% Yield	Solvent of Crystallization	M.P. Free Base	M.P. of HCL Salt	Mole Formula	Calculated Mole Weight	Analysis					
								Calculated			Formed		
								C	H	N	C	H	N
A	3,4-Cl_2-C_6H_3-CH_2-	98	MeOH	194-196°	230-233°; d	$C_{13}H_{14}N_6Cl_2$	325.2	48.00	4.33	25.82	47.80	4.42	25.69
B	2,4-Cl_2-C_6H_3-CH_2-	92	$CHCl_3$ or DMSO-H_2O	155-157°	214-216°; d	$C_{13}H_{14}N_6Cl_2H_2O$	325.2	45.50	4.70	24.50	45.98	4.81	24.69
C	4-Cl_2-C_6H_4-CH_2-	97	EtOH	197-199°	240-241°; d	$C_{13}H_{15}N_6Cl\cdot 2HCl$	290.76	42.92	4.68	23.10	42.99	5.01	22.53
D	3-CF_3-C_6H_4-CH_2-	98	$CHCl_3$ or DMSO-H_2O	158-159°	213-215°; d	$C_{14}H_{15}N_6F_3\cdot 2HCL\cdot 2H_2O$	324.31	38.79	4.80	19.40	38.55	4.26	19.23
E	2-Cl-C_6H_4-CH_2-CH_2-	62.4	MeOH or MeOH-Et_2O	186-188°	212-217°	$C_{14}H_{17}N_6CL\cdot CH_3OH$	304.78	53.48	6.28	24.95	53.37	6.25	25.09
F	4-CL-C_6H_4-CH_2-CH_2-	76	MeOH	187-193°	212-217°; d	$C_{14}H_{17}N_6Cl\cdot CH_3OH$	304.78	53.48	6.28	24.95	53.82	6.31	25.07
G	3-Cl_2-C_6H_4-CH_2 CH_2-	96	MeOH	104-105.5°	206-210°; d	$C_{14}H_{17}N_6Cl\cdot CH_3OH$	304.78	53.48	6.28	24.95	53.33	6.21	25.28
H	3-CF_3-C_6H_4-CH_2CH_2-	80.6	MeOH or MeOH-H_2O	112-114°	--	$C_{15}H_{17}N_6F_3$	338.24	51.89	5.75	22.70	51.44	5.72	22.93
I	2,4-Cl_2-C_6H_3-CH_2CH_2-	80.2	$CHCl_3$ or DMSO-H_2O	186-188°	--	$C_{14}H_{16}N_6Cl_2$	339.23	49.75	4.74	24.69	49.73	4.77	24.72
J	2,6-Cl_2-C_6H_3-CH_2-CH_2-	76.1	MeOH-EtOH	200-202°	--	$C_{14}H_{16}N_6Cl_2$	339.23	49.75	4.74	24.69	49.57	4.75	24.78
K	2,6-Cl_2-C_6H_3-CH_2-O-	42	MeOH	230-231.5°	236.5-238°; d	$C_{13}H_{14}N_6Cl_2O$	341.2	45.75	4.11	24.63	45.64	4.14	24.58
L	2,4-Cl_2-C_6H_3-CH_2O-	43	EtOH	208-209.5°	239-241.5°; d	$C_{13}H_{14}N_6Cl_2O$	341.2	45.75	4.11	24.63	45.76	4.09	24.67
M	4-Cl_2-C_6H_4-CH_2-O-	56	MeOH	205-206.5°	251-253°; d	$C_{13}H_{15}N_6ClO$	306.76	50.90	4.89	27.40	51.02	5.08	27.41
N	3-CF_3-C_6H_4-CH_2-O-	37	$CHCl_3$-MeOH	200-202°	247-249° d	$C_{14}H_{15}N_6F_3O$	340.31	49.41	4.41	24.70	49.64	4.61	24.78
O	2,4-Cl_2-C_6H_3-O-CH_2-CH_2-O-	50	MeOH	180-182.5°	--	$C_{14}H_{16}N_6Cl_2O_2$	371.0	45.28	4.31	22.64	45.04	4.55	22.13
P	4-CL-C_6H_4-CH_2CH_2-O-	62	MeOH-H_2O	187-189°	--	$C_{14}H_{17}N_6ClO$	320.5	52.46	5.30	26.21	52.48	5.31	26.25
Q*	HO				224° d	$C_6H_{10}N_6O\cdot 1\frac{1}{2}HCl$	225.5	31.89	5.00	37.20	32.26	4.96	37.09
R*	$(2,4\text{-}Cl_2\text{-}C_6H_3\text{-}O)_2CH_2$			103-4°		$C_{13}H_8Cl_4O_2$	338.0	46.39	2.39		46.25	2.40	
S*	$(3\text{-}CF_3\text{-}C_6H_4\text{-}O)_2\text{-}CH_2$			52-3°		$C_{15}H_{10}F_6O_2$	336.2	53.58	3.00		53.67	2.96	

*See Addendum

TABLE 2

SUMMARY OF BIOLOGICAL SCREENING RESULTS

Report Identification No.	Submitter Compound No.	W. R. Bottle No.	Screening Results	
			Antimalarial	Antitrypanosomal
A	SMS - 1	BH84175	-	
B	SMS - 5	BH84193	-	
		BH89063		-
C	SMS - 2	BH84184	-	
D	SMS - 12	BH84513	-	-
E	SMS - 20	BJ07100	-	-
F	SMS - 15	BJ07084	-	-
G	SMS - 18	BJ07093	-	-
H	SMS - 24	BJ09971	-	
I	SMS - 21	BJ07119	-	
J	SMS - 19	BJ01993	-	-
K	SMS - 6	BH86508	-	
		BH89072		-
L	SMS - 7	BH86517	-	
		BH89081		-
M	SMS - 8	BH86526	-	
		BH89090		-
N	SMS - 9	BH86535	-	
O	SMS - 23	BJ07128	-	-
P	SMS - 22	BJ09471		
Q*	DDK - 1	BJ58036	-	-
R*	SMS - 28	BJ58018	-	
S*	SMS - 29	BJ58027	-	

*See Addendum

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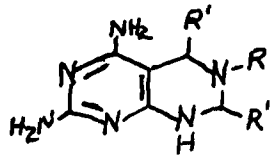
Addendum

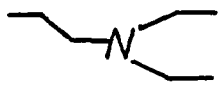
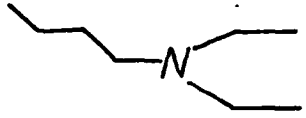
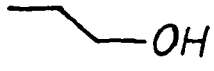
Because of personnel changes since this Annual Report was compiled the amount and type of laboratory effort has been disrupted. The consequence of this situation would be a somewhat disjointed report. Rather then providing such a report we requested, and were granted approval, the opportunity of adding to the recently approved Annual Report.

This addition comprises two parts. The first is a supplemental list of those compounds which have been recently prepared, submitted for screening and for which biological data exists. These compounds have been added to Tables 1 and 2 with appropriate chemical and biological data. These additions are marked by an asterisk. Compounds labeled R and S are intermediates and do not have the same general structure as other numbers on the list. In the column designated R complete structural formulas are given for these two examples.

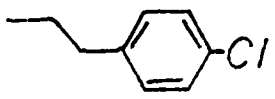
The second part consists of a collection of compounds which are actively under investigation. This group is not covered in previous Annual Reports and represents our most immediate goals. Comments are offered for each to indicate the status of work effort. These may be found in Appendix 1.

APPENDIX 1



Chemical Name	R	R'	Comments
2,4-diamino-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine	H	H	There have been two brief efforts at the synthesis of this substance. Both were unsuccessful. As time permits we intend to return to this problem since this substance can be a valuable intermediate
6-(diethylaminoethyl)-2,4-diamino-5,6,7,8-tetrahydropyrimido[4,5-d] pyrimidine		H	This compound has been synthesized albeit in small quantity. Product identification has been ascertained through NMR spectra. *Difficulties with obtaining pure starting* materials have delayed this work. The effort will be renewed shortly.
6-(diethylaminopropyl)-2,4-diamino-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine		H	This compound has also been prepared in small quantity sufficient for spectral identification. As with the previous example further work is planned to prepare sufficient quantity for screening.
6-(2-hydroxyethyl)-2,4-diamino-5,6,7,8-tetrahydropyrimido-[4,5-d]pyrimidine		H	This compound has already been synthesized. Complete characterization was not achieved because of latent instability. Because of this the compound was submitted for screening in person. Screening results are not available at this time.

Appendix 1 (Cont'd)

Chemical Name	R	R'	Comments
6-(4-chlorobenzyl)-3,4-diamino-5,7-dimethyl-5,6,7,8-tetrahydropyrimidc[4,5-d]pyrimidine		CH_3	Preliminary results with this preparation indicate that the desired product was obtained, possibly in a single stereochemical arrangement. This problem is under active investigation at present.
6-[2-(4-chlorophenyl)-ethyl-2,4-diamino-5,7-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine		CH_3	The approach of the previous example was extended to the ethyl analog. Laboratory work in this case is continuing as well and preliminary chromatographic analysis indicates that this preparation may also be achieved.